ONLINE-ONLY MATERIALS

Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis

Revision Date: 22 September 2010

Theodore J. Iwashyna, MD, PhD
E. Wesley Ely, MD, MPH
Dylan M. Smith, PhD
Kenneth M. Langa, MD, PhD

CONTENTS:

1. Cover Page

2. eMETHODS: Appendix on Statistical Methods for Primary Analysis

3. eTable 1: Demographics of All Patients Hospitalized with Severe Sepsis, Stratified by Baseline Physical Functioning

4. eTable 2: Risk Factors for Cognitive Impairment

5. eTable 3: Comparing the Association of Severe Sepsis and Non-Sepsis General Hospitalizations with the Acquisition of New Functional Limitations, by Functional Class at Baseline

6. eTable 4: Comparing the Association of Severe Sepsis and Non-Sepsis General Hospitalizations with Moderate/Severe Cognitive Impairment

7. eTable 5: Subgroup Analysis: Severe Sepsis and Moderate/Severe Cognitive Impairment Among Survivors Who Were Age 65 and Above at Baseline

8. eTable 6: Subgroup Analysis: Acquisition of New Functional Limitations Before and After Sepsis Among Survivors Who Were Age 65 and Above at Baseline, by Functional Class at Baseline

9. eTable 7: Sensitivity Analysis: Acquisition of New Functional Limitations Before and After Sepsis Among Survivors, by Functional Class at Baseline, Including all HRS Surveys 1992-2006

10. eTable 8: Subgroup Analysis: Severe Sepsis and Moderate/Severe Cognitive Impairment Among Survivors, Only First Hospitalizations for Severe Sepsis in Cohort

11. eTable 9: Subgroup Analysis: Acquisition of New Functional Limitations Before and After Sepsis Among Survivors, by Functional Class at Baseline, Only First Hospitalizations for Severe Sepsis in Cohort

12. eFigure 1: Survival by Baseline Cognitive and Physical Functioning for Entire Cohort of Patients with Severe Sepsis

13. References for Online-Only Material

eMETHODS: Appendix on Statistical Methods for Primary Analysis

For our analyses of physical disability, our primary outcome variable was the number of ADL and IADL limitations of the patient, ranging from 0 to 11. For multivariable models, we used fixed effects linear regression to analyze the impact of severe sepsis on the incidence of moderate/severe cognitive impairment, implemented using *xtreg, fe* in Stata 10.1. In this analytic approach, patients served as their own controls. *Only within-person* variation *over time* was used to estimate the effect of severe sepsis; in the panel data literature, this is known as a "fixed effects" approach. [1,2] (Note that the term "fixed effect" is also, confusingly, sometimes used in the biostatistical literature on regression with a distinct meaning.[3]) A separate intercept was estimated for each hospitalization. This approach controlled for all characteristics of the patient that did not change over time, without explicitly measuring such characteristics. No parameters or limitations were set on the hospitalization-specific intercept terms, and therefore such models were very flexible.

Our data was organized at the survey level, one line per survey per severe sepsis hospitalization. Our independent variable was time from admission date for severe sepsis, measured to the day of each survey. We allowed the rate of developing I/ADL limitations per unit time to change from before sepsis to afterwards by parameterizing time as a linear spline with a knot at the day of admission for the hospitalization for severe sepsis. We further measured a point change in the odds of functional limitations associated with sepsis with an additional dichotomous indicator variable, distinguishing surveys prior to from surveys after the severe sepsis date of hospitalization admission.

Having used fixed effect regressions, there were two particularly important potential problems, for which we tested. The first potential problem was that because these analyses used only within-patient variation, they might have relatively larger standard errors than other approaches. In our case, we saw no evidence of clinically significant results that appeared too imprecisely measured to be statistically significant. The second potential problem was that such models might "overfit" the data as a result of the large number of hospitalization-specific nuisance parameters that were estimated. In order to test for this, we reran the analyses in presented in Table 2 and 3 across 100 bootstrapped re-samples, [4,5] and found no greater variation in our estimates than was expected from the reported confidence intervals.

Finally, reasonable analysts may prefer an alternative approach to flexibly controlling for hospitalization-specific characteristics, sometimes called "random effects" models. In such models, hospitalization-specific intercepts are again estimated, but in this case they are assumed to be drawn from a distribution for which a mean and variance are estimated. [2] This approach requires far fewer parameters to be estimated, but imposes parametric restrictions on the distribution of hospitalization-specific intercepts that may or may not be valid. We prefer the more flexible fixed effects approach. However, we replicated our analyses as random effects models using *xtmixed* and with *GLLAMM* in Stata 10.1 and found substantively identical results. We conducted further confirmatory analyses using an ordered logistic regression with the dependent variable as 12 levels of functional impairment and a random-intercept model, and again found similar results.

For our analyses of cognition, our primary outcome variable was level of cognitive impairment. For multivariable models, we used conditional logistic regression to analyze the impact of severe sepsis on the incidence of moderate/severe cognitive impairment, implemented using *clogit* in Stata 10.1. As for disability, this approach used *only within-person variation over time* to estimate the effect of severe sepsis. We used the same spline parameterization. For these analyses we also conducted the bootstrap replications to test for over-fitting, and found no greater variation in our estimates than was expected from the reported confidence intervals. We also replicated our cognition analyses as random effects models using *GLLAMM* in Stata 10.1 and found substantively identical results. We conducted further confirmatory analyses using an ordered logistic regression with 3 levels of cognitive impairment and a random-intercept model, and again found similar results.

101 **eTable 1: Demographics of All Patients Hospitalized with Severe Sepsis,**
102 **Stratified by Baseline Physical Functioning (n= 1,520 hospitalizations)**
103

	No Limits	Mild / Moderate Limits	Severe Limits
n (hospitalizations)	529	476	515
Male (%)	299 (57%)	225 (47%)	189 (37%)
Black (%)	87 (16%)	88 (18%)	141 (27%)
Hispanic (%)	31 (6%)	30 (6%)	43 (8%)
Age at Sepsis (years)	76.7	78.6	80.6
Length of Stay (days)	11.6	11.1	10.7
Required Mechanical Ventilation	160 (30%)	131 (28%)	140 (27%)
Required Dialysis	25 (4.7%)	22 (4.6%)	45 (8.7%)
Used an Intensive Care Unit	284 (54%)	230 (48%)	233 (45%)
Underwent Major Surgery	132 (25%)	84 (18%)	63 (12%)
Charlson Score (mean)	2.12	2.38	2.11
Alive 90 Days After Admission *	63%	61%	52%
Organ Dysfunction Score (mean)	1.27	1.26	1.25
Acute Cardiovascular Dysfunction	138 (26%)	139 (29%)	140 (27%)
Acute Neurologic Dysfunction	38 (7%)	40 (8%)	45 (9%)
Acute Hematologic Dysfunction	114 (22%)	86 (18%)	77 (15%)
Acute Hepatic Dysfunction	7 (1%)	4 (1%)	5 (1%)
Acute Renal Dysfunction	217 (41%)	202 (42%)	236 (46%)
Acute Respiratory Dysfunction	160 (30%)	131 (28%)	140 (27%)
Baseline Cognition Normal	504 (95.3%)	439 (92.2%)	327 (63.5%)
Baseline Mild Cognitive Impairment	20 (3.8%)	25 (5.3%)	73 (14.2%)
Baseline Moderate/Severe Cognitive Impairment	5 (1.0%)	12 (2.5%)	115 (22.3%)
Baseline ADL Deficiencies	0	1.2	4.0
Baseline IADL Deficiencies	0	0.6	3.1
Proxy Respondent at Baseline	34 (6%)	70 (15%)	245 (48%)
Proxy Respondent at First Post-Sepsis Survey	46 (17%)	47 (24%)	87 (55%)

104 * Kaplan-Meier estimate.
105

106

107　**eTable 2: Risk Factors for Cognitive Impairment**
108　For all patients who developed severe sepsis, stratified by their baseline functional status.
109

Baseline Functioning:	No Limits	Mild / Moderate Limits	Severe Limits
n (hospitalizations)	529	476	515
Self-Reported Chronic Conditions			
Stroke	8%	18%	39%
Diabetes	26%	28%	37%
Hypertension	62%	68%	69%
Cardiac Disease	40%	46%	55%
Lung Disease	17%	25%	19%
CES-D Score (Mean)	1.8	2.17	2.38
Alcohol Intake (Days per week)			
0	77%	83%	93%
<1	3%	4%	2%
1 to 2	5%	3%	1%
>2	15%	10%	3%
Smoking Status			
Never	27%	37%	44%
Former	57%	50%	45%
Current	16%	14%	11%
Net Worth (Mean)	$292,018	$219,357	$139,125
Education			
High School or Less	37%	42%	55%
Some College	33%	37%	27%
College Graduate	30%	20%	19%

110

111
112

113 **eTable 3: Comparing the Association of Severe Sepsis and Non-Sepsis**
114 **General Hospitalizations with the Acquisition of New Functional**
115 **Limitations, by Functional Class at Baseline**
116
117 As in Table 3, a within-person regression was estimated, but in this case in a synthetic cohort
118 combining the severe sepsis survivors and the non-sepsis general hospitalization survivors. The
119 continuous outcome variable was the number of functional limitations. Interaction terms between
120 time and severe sepsis were estimated to measure the marginal effect of severe sepsis beyond
121 that expected from a general hospitalization. Note that main effects of this synthetic cohort may
122 not generalize to any population of interest. The marginal effects, or differences, are the results of
123 interest that answer the question: "how different is the association with severe sepsis than the
124 association with non-sepsis general hospitalization?"
125
126 95% confidence intervals are in parentheses. The absence of an association is indicated by the
127 acquisition of 0 new functional limitations.
128

| | Functional Class at Baseline | | |
	No Limits	Mild/Moderate Limits	Severe Limits
Before Hospitalization	-0.025	0.16	0.71
(per year)	(-0.037,-0.012)	(0.12,0.20)	(0.60,0.81)
p-value	$p < 0.001$	$p < 0.001$	$p < 0.001$
Marginal Effect of Severe Sepsis for	0.045	-0.051	0.13
Pre-Hospitalization Change	(-0.019,0.11)	(-0.15,0.050)	(-0.050,0.31)
p-value for interaction	$p = 0.169$	$p = 0.323$	$p = 0.155$
Effect of Hospitalization	0.48	0.43	-0.47
	(0.39,0.56)	(0.22,0.63)	(-0.83,-0.11)
p-value	$p < 0.001$	$p < 0.001$	$p = 0.010$
Marginal Effect of Hospitalization for	1.10	1.07	0.51
Severe Sepsis on Acute Change	(0.53,1.67)	(0.43,1.71)	(-0.34,1.35)
p-value for interaction	$p < 0.001$	$p = 0.001$	$p = 0.240$
After Hospitalization	0.21	0.27	0.10
(per year)	(0.18,0.24)	(0.21,0.33)	(0.0040,0.20)
p-value	$p < 0.001$	$p < 0.001$	$p = 0.041$
Marginal Effect of Severe Sepsis for	-0.018	0.24	0.056
Post-Hospitalization Change	(-0.24,0.20)	(-0.027,0.50)	(-0.30,0.41)
p-value for interaction	$p = 0.873$	$p = 0.079$	$p = 0.756$

129
130
131
132

133 **eTable 4: Comparing the Association of Severe Sepsis and Non-Sepsis**
134 **General Hospitalizations with Moderate/Severe Cognitive Impairment**
135
136 As in Table 2, a within-person regression was estimated, but in this case in a synthetic cohort
137 combining the severe sepsis survivors and the non-sepsis general hospitalization survivors. The
138 dichotomous outcome variable was the presence or absence of moderate/severe cognitive
139 impairment at that wave. Interaction terms were estimated between time and severe sepsis to
140 measure the marginal effect of severe sepsis beyond that expected from the general
141 hospitalization. Note that main effects of this synthetic cohort may not generalize to any
142 population of interest. The marginal effects, or differences, are the results of interest that answer
143 the question: "how different is the association with severe sepsis than the association with non-
144 sepsis general hospitalization?"
145
146 95% confidence intervals are in parentheses. The absence of an association is indicated by an
147 odds ratio of 1 for the development of moderate/severe cognitive impairment.
148

	Odds Ratio	95% CI	p-value
Before Hospitalization (per additional year)	1.42	(1.24,1.63)	$p < 0.001$
Marginal Effect of Severe Sepsis (per year) *	0.95	(0.75,1.19)	$p = 0.651$
Effect of Hospitalization	1.15	(0.80,1.67)	$p = 0.451$
Marginal Effect of Severe Sepsis Hospitalization *	2.89	(1.26,6.64)	$p = 0.012$
After Hospitalization (per additional year)	1.78	(1.64,1.94)	$p < 0.001$
Marginal Effect of Severe Sepsis (per year)*	0.94	(0.72,1.24)	$p = 0.685$

149 * Key interaction terms of interest
150

151 **eTable 5: Subgroup Analysis: Severe Sepsis and Moderate/Severe**
152 **Cognitive Impairment Among Survivors Who Were Age 65 and Above at**
153 **Baseline**
154
155 Compare to Table 2.
156

	Odds Ratio	95% CI	p-value
Before Sepsis (per additional year)	1.37	(1.12,1.69)	p = 0.003
Effect of Sepsis	3.67	(1.67,8.07)	p = 0.001
After Sepsis (per additional year)	1.79	(1.32,2.43)	p < 0.001

157
158

159 **eTable 6: Subgroup Analysis: Acquisition of New Functional Limitations**
160 **Before and After Sepsis Among Survivors Who Were Age 65 and Above at**
161 **Baseline, by Functional Class at Baseline**
162
163 Compare to Table 3. Confidence intervals are in parentheses.
164
165   The within-patient R^2 were 0.25 for the no limitation group, 0.37 for those with mild/moderate
166 baseline limitations, and 0.46 for those with severe baseline limitations.

	Functional Class at Baseline		
	No Limits	**Mild/Moderate Limits**	**Severe Limits**
	n = 261	n = 178	n = 150
Before Sepsis	0.025	0.14	0.84
(per year)	(-0.043,0.094)	(0.06,0.22)	(0.68,1.00)
p-value	$p = 0.470$	$p = 0.001$	$p < 0.001$
Effect of Sepsis	1.59	1.46	-0.008
	(1.00,2.19)	(0.78,2.14)	(-0.83,0.81)
p-value	$p < 0.001$	$p < 0.001$	$p = 0.984$
After Sepsis	0.11	0.58	0.22
(per year)	(-0.14,0.36)	(0.27,0.89)	(-0.15,0.60)
p-value	$p = 0.098$	$p < 0.001$	$p = 0.237$

167
168

169 **eTable 7: Sensitivity Analysis: Acquisition of New Functional Limitations**
170 **Before and After Sepsis Among Survivors, by Functional Class at Baseline,**
171 **Including all HRS Surveys 1992-2006**
172
173 Compare to Table 3. Confidence intervals are in parentheses.
174
175 The within-patient R^2 were 0.27 for the no limitation group, 0.37 for those with mild/moderate
176 baseline limitations, and 0.49 for those with severe baseline limitations.

| | Functional Class at Baseline | | |
	No Limits	Mild/Moderate Limits	Severe Limits
	n = 368	n = 243	n = 218
Before Sepsis	0.033	0.14	0.66
(per year)	(-0.010,0.075)	(0.086,0.19)	(0.60,0.72)
p-value	$p = 0.130$	$p < 0.001$	$p = 0.000$
Effect of Sepsis	1.61	1.82	0.53
	(1.32,1.90)	(1.45,2.20)	(0.0044,1.05)
p-value	$p < 0.001$	$p < 0.001$	$p = 0.048$
After Sepsis	0.20	0.27	0.065
(per year)	(0.13,0.27)	(0.16,0.37)	(-0.15,0.28)
p-value	$p < 0.001$	$p < 0.001$	$p = 0.546$

177
178
179
180

181   **eTable 8: Subgroup Analysis: Severe Sepsis and Moderate/Severe**
182   **Cognitive Impairment Among Survivors, Only First Hospitalizations for**
183   **Severe Sepsis in Cohort**
184
185   Compare to Table 2.
186

	Odds Ratio	95% CI	p-value
Before Sepsis (per additional year)	1.30	(1.06,1.61)	p = 0.012
Effect of Sepsis	3.54	(1.65,7.63)	p = 0.001
After Sepsis (per additional year)	1.65	(1.29,2.11)	p < 0.001

187
188

189 **eTable 9: Subgroup Analysis: Acquisition of New Functional Limitations**
190 **Before and After Sepsis Among Survivors, by Functional Class at Baseline,**
191 **Only First Hospitalizations for Severe Sepsis in Cohort**
192
193 Compare to Table 3. Confidence intervals are in parentheses.
194
195 The within-patient R^2 were 0.24 for the no limitation group, 0.38 for those with mild/moderate
196 baseline limitations, and 0.39 for those with severe baseline limitations.

| | Functional Class at Baseline | | |
	No Limits	Mild/Moderate Limits	Severe Limits
	n = 228	n = 167	n = 121
Before Sepsis	0.0027	0.14	0.76
(per year)	(-0.049,0.054)	(0.054,0.22)	(0.58,0.94)
p-value	p = 0.919	p = 0.001	p < 0.001
Effect of Sepsis	1.61	1.54	-0.057
	(1.07,2.15)	(0.92,2.16)	(-0.84,0.73)
p-value	p < 0.000	p < 0.000	p = 0.885
After Sepsis	0.15	0.47	0.22
(per year)	(-0.033,0.33)	(0.22,0.72)	(-0.10,0.54)
p-value	p = 0.108	p = 0.000	p = 0.184

197
198

199 **eFigure 1: Survival by Baseline Cognitive and Physical Functioning for**
200 **Entire Cohort of Patients with Severe Sepsis.**
201
202 These data show that patients with any degree of cognitive or physical impairment at baseline
203 have substantially worse survival after severe sepsis than do those with normal cognitive or
204 physical functioning. (*p* < 0.0001 by log-rank test, confirmed in Cox regression)
205
206 *Methodological Note:* Death dates were obtained in the HRS from both linkage to the National
207 Death Index and detailed survey follow-up with next of kin. Censoring occurred on the date of
208 last known alive contact from the HRS. Unadjusted survival analyses were done using the
209 Kaplan-Meier method.
210

211

212
213
214
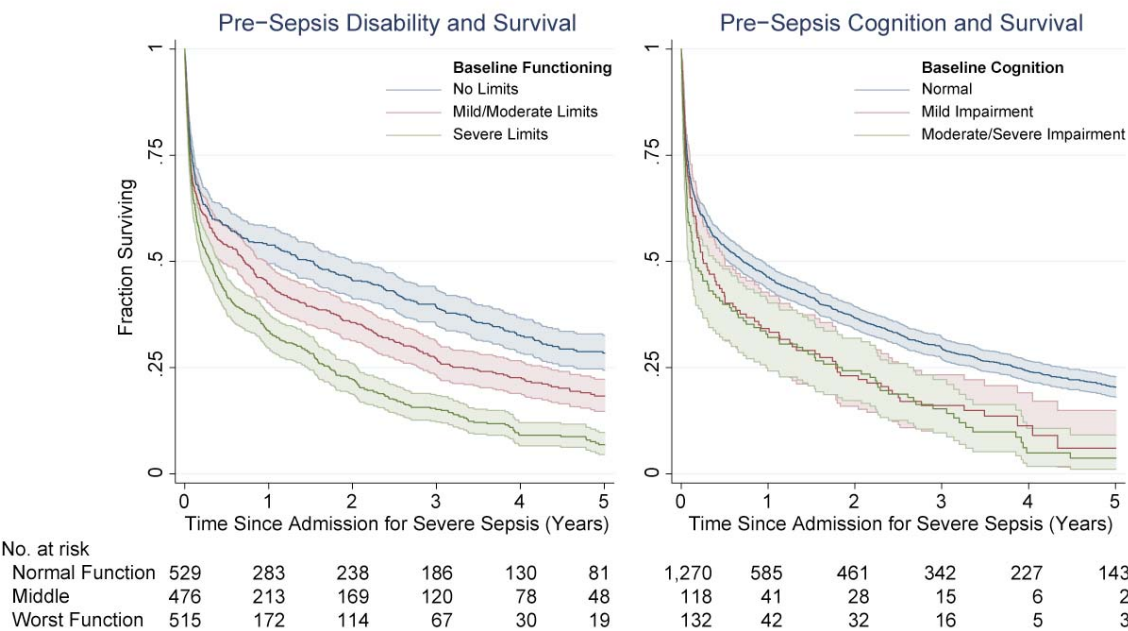
215 **References**
216
217 **1.**   Allison PD. *Fixed Effects Regression Methods for Longitudinal Data Using SAS*: SAS Publishing;
218   2005.
219 **2.**   Rabe-Hesketh S, Skrondal A. *Multilevel and Longitudinal Modeling Using Stata*. College Station,
220   Texas: Stata Press; 2008.
221 **3.**   Farewell VT. Fixed Effects. In: Armitage P, ed. *Encyclopedia of Biostatistics.* Vol 2. New York:
222   John Wiley; 1998:1533.
223 **4.**   Good PI. *Resampling Methods.* Boston: Birkhauser; 2006.
224 **5.**   Mooney CZ, Duval R. *Bootstrapping: A Nonparametric Approach to Statistical Inference.*
225   Newbury Park: Sage Publications; 1993.
226
227